

# Ixekizumab for treating moderate to severe plaque psoriasis

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Ixekizumab is recommended as an option for treating plaque psoriasis in adults, only if:
- the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - the disease has not responded to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them, and
  - the company provides the drug with the discount agreed in the patient access scheme.
- 1.2 Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
- a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.
- 1.3 When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.
- 1.4 When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.
- 1.5 These recommendations are not intended to affect treatment with ixekizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them

before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

<b>Description of the technology</b>	Ixekizumab (Taltz, Eli Lilly) is an antibody that inhibits IL-17A (interleukin-17A, a pro-inflammatory cytokine).
<b>Marketing authorisation</b>	Ixekizumab is 'indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy'.
<b>Adverse reactions</b>	The most common adverse reactions with ixekizumab in clinical trials were upper respiratory tract infection and injection-site reactions (occurring in at least 10% of people). For full details of adverse reactions and contraindications, see the summary of product characteristics.
<b>Recommended dose and schedule</b>	By subcutaneous injection; 160 mg at week 0, followed by 80 mg every 2 weeks until week 12. After week 12, 80 mg every 4 weeks.
<b>Price</b>	The list price is £1,125 for 80 mg, and £2,250 for 2×80 mg. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ixekizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

## 3 Evidence

The appraisal committee ([section 6](#)) considered evidence submitted by Eli Lilly and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

## 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ixekizumab, having considered evidence on the nature of moderate to severe psoriasis and the value placed on the benefits of ixekizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The committee heard about the experience of people with psoriasis. It acknowledged that psoriasis can be a debilitating disease that affects all aspects of a person's life: physically, psychologically and socially. It noted that clearing symptoms with treatments associated with few or manageable side effects is important to people with psoriasis, as is having a choice of treatments.

### Treatment pathway

- 4.2 The committee heard from the clinical experts that biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin and methotrexate) or when these treatments are contraindicated or not tolerated. It heard from the clinical experts that, because there are long-term data available for other biologicals and clinicians are familiar with using them, ixekizumab was likely to be offered to 2 groups:

- patients who had already had a biological treatment to which their disease had not responded
- patients for whom other biological agents were contraindicated.

The committee heard that clinicians might offer ixekizumab as a first biological treatment when doctors become more familiar with the treatment and there are more long-term data. The committee accepted that ixekizumab was likely to be used as a second biological treatment in a sequence of biological agents, but could be used as a first biological treatment for people for whom other biological agents are not appropriate. The committee also accepted that over



time as more data become available, ixekizumab could replace older, less effective biologicals as a first biological treatment.

## Comparators

- 4.3 The committee was aware that the company's clinical evidence and economic model compared ixekizumab with biological treatments (etanercept, adalimumab, ustekinumab, secukinumab and infliximab), and only included comparisons with standard systemic therapies in scenario analyses. The committee considered that this was appropriate because it agreed with the company that in clinical practice, ixekizumab would be offered at the same place in the treatment pathway as the existing biological treatments (see section 4.2). The committee therefore concluded that the most appropriate comparators for ixekizumab were other biological treatments.

## Clinical effectiveness

### Generalisability of the trial populations

- 4.4 The committee noted that the evidence for ixekizumab mostly came from 3 trials: UNCOVER-1, -2 and -3, which were double-blinded, randomised controlled trials that included 3,866 patients. UNCOVER-1 compared ixekizumab with placebo, and UNCOVER-2 and -3 compared ixekizumab with placebo and with etanercept. The primary outcome was Psoriasis Area and Severity Index (PASI) 75, which is a 75% reduction in the PASI score from when treatment started, measured at 12 weeks (the end of the induction period).
- 4.5 The committee was aware that the trials included patients with a PASI score of 12 or more and that in previous appraisals of technologies for treating psoriasis, a PASI score of 10 or more had been defined as severe disease. The committee heard from the clinical experts that the PASI is a composite measure of disease severity that combines the extent of the body surface area involved and the severity of the redness, thickness and scaling in each area. It understood that higher values represent increased severity. The committee also understood that the trials

included patients with Dermatology Life Quality Index (DLQI) scores ranging from 0 to 30, and that in previous NICE appraisals of technologies for treating psoriasis, a DLQI score of more than 10 had been defined as severe disease. It was aware that the DLQI is a questionnaire that aims to measure how much psoriasis affects the life of people who have it. It heard from the company that the trial eligibility criteria had also included a static Physician Global Assessment score of 3 or more, where scores of 3, 4 and 5 are defined as moderate, severe and very severe disease, respectively. The committee heard from the clinical experts that in clinical practice disease severity is rarely defined in this way. The committee heard from the clinical experts that patients being considered for biological treatment would tend to have a PASI score of 10 or 12 or above, and that the patients in the UNCOVER trials were representative of patients seen in the NHS who would be considered for biological treatment.

- 4.6 The committee noted that the population in the trials and the marketing authorisation for ixekizumab included people who are candidates for systemic therapy, which includes both non-biological and biological treatments. It noted that the UNCOVER trials included patients who had never had systemic treatment, had had systemic treatment, or had already had biological treatment. Overall, the committee concluded that although previous treatment for trial participants varied, the populations of the UNCOVER trials were likely to be generalisable to patients in the NHS who would be considered for biological treatment, and were appropriate for decision-making on the clinical effectiveness of ixekizumab.

## **Ixekizumab compared with placebo and etanercept**

- 4.7 The committee noted that patients randomised to ixekizumab had clinically and statistically significantly higher PASI 75 response rates at week 12 than placebo and etanercept. The odds ratios for ixekizumab producing a higher PASI 75 response rate at week 12 are detailed in table 1.

### **Table 1 Odds ratios for ixekizumab producing higher PASI 75**

## response rate at week 12

UNCOVER-1	UNCOVER-2	UNCOVER-3
<b>Compared with placebo</b>		
223.94 95% CI 125.05 to 401.03	997.29 95% CI 173.11 to 5,745.5	72.29 95% CI 36.11 to 144.73
<b>Compared with etanercept</b>		
N/A	13.28 95% CI 8.66 to 20.34	6.46 95% CI 4.42 to 9.45
Abbreviations: CI, confidence interval; N/A, not applicable.		

The committee noted that the dose of etanercept given in the trials was double that which is recommended in NICE's technology appraisal guidance on [etanercept and efalizumab for the treatment of adults with psoriasis](#), and was considered by the clinicians to be more effective than lower doses of etanercept. Therefore the committee considered that the odds ratios could underestimate the treatment effect of ixekizumab compared with etanercept. The committee concluded that ixekizumab was more clinically effective than placebo and etanercept.

## Ixekizumab in patients who have already had biological treatment

4.8 The committee noted that the benefit of treatment with ixekizumab compared with placebo and etanercept could be seen in the subgroup of patients who had already had biological treatment, as well as those who had not previously had biological treatment. It heard that the company did a test for interaction that showed little difference between the results of the trials across subgroups defined by baseline disease severity and previous biological treatment. The committee noted that the trials were not powered to detect statistically significant differences between subgroups, and so it could not be certain that the treatment effect did not differ across subgroups, however it agreed there was no evidence of a subgroup effect. The committee heard from the clinical experts that biological treatments generally work less well in patients who have already had a biological treatment, but that it depends on the particular biological treatment, and factors such as disease severity. The

committee therefore concluded that, based on the data available, ixekizumab was more effective than etanercept or placebo both for patients who had previously had biological treatment and for those who had not.

## Network meta-analysis results

4.9 The committee discussed the company's network meta-analysis that compared ixekizumab with adalimumab, ustekinumab, secukinumab and infliximab indirectly. The results showed that the relative risk of ixekizumab achieving a PASI 75 response at 12 weeks was significantly higher than that of all the biological treatment comparators except infliximab.

- The committee noted that the relative risk of secukinumab achieving a PASI 75 response compared with placebo and other biological treatments was lower than that seen in NICE's technology appraisal guidance on [secukinumab for treating moderate to severe plaque psoriasis](#). It heard from the company that it had included trials of secukinumab in its analysis that had not been included in the secukinumab appraisal.
- The committee understood from the clinical experts that some of the biological treatments are known to work less well if they are used after another biological treatment. It heard from the company that it was not feasible to analyse the data separately for patients who had previously had biological treatment and those who had not because some of the trials included in the network meta-analysis did not report information for these groups separately. The committee concluded that, because the network meta-analysis reflected a mixture of people who had and had not already had biological treatments, it was uncertain how generalisable the results were to ixekizumab being given as a first or second biological treatment in a sequence of biological treatments (see [section 4.2](#)).
- The committee considered the comment received during consultation noting that data from the British Association of Dermatologists' Biologic Intervention Register showed higher PASI scores for adalimumab than those presented to the committee. The committee recognised that network meta-analyses use trial-based estimates of relative treatment effects rather than registry data. Furthermore, the patients in the registry may differ from those included in the

trials. The committee noted the evidence review group's (ERG's) comment that the results of the network meta-analysis were similar to those presented in previous technology appraisals for psoriasis. Because of this, the committee agreed that the network meta-analysis remained the more reliable estimate for decision-making.

Acknowledging these uncertainties, the committee concluded that the network meta-analysis showed that ixekizumab was more clinically effective than adalimumab and ustekinumab, and agreed it was likely that ixekizumab was similarly effective compared with secukinumab and infliximab.

## Adverse events

4.10 The committee was aware that the rates of serious adverse events including non-melanoma skin cancer, malignancies other than non-melanoma skin cancer, and severe infection, were very low, and that most of the adverse events related to treatment were mild to moderately severe and did not lead to stopping treatment. It heard from the clinical experts that serious infection was the main concern with biologicals, but that treatment was generally well tolerated. The committee concluded that the tolerability of ixekizumab was similar to that for other biological treatments approved for treating psoriasis.

## Cost effectiveness

### Model structure

4.11 The committee considered the Markov state transition model the company used to model the cost effectiveness of ixekizumab. It modelled 7 biological treatment sequences and contained 4 health states:

- **Induction period:** All patients start in this health state and have treatment in the induction period. Moving from induction to maintenance occurs when a patient's disease has achieved a 75% reduction in PASI score at the end of the induction period. If their disease responds inadequately, patients move on to the next treatment in the sequence.

- **Maintenance:** Patients stay on treatment until it is stopped for any reason. After treatment stops, patients move to the induction phase of the next treatment in the sequence.
- **Best supportive care:** Patients enter this health state after having up to 3 biological treatments. Patients can have non-biological therapies and maintain a level of response until death.
- **Death:** Moving to this state is possible from any of the above states. The general population mortality rate is applied.

4.12 The committee noted that the ERG considered the treatment sequencing approach to be better than comparing individual treatments because it more closely reflected clinical practice. It noted that the model represented both patients who had never had systemic treatments, and those who had already had biological treatment. The committee concluded that the company's model structure reflected clinical practice.

4.13 The committee understood that the company had used market share information to determine the most commonly used treatment sequences in the NHS. Each of the 7 biological treatments was modelled first in a sequence of 3 biologicals, as follows:

- ixekizumab, ustekinumab (90 mg), infliximab
- adalimumab, ustekinumab (90 mg), infliximab
- etanercept, ustekinumab (90 mg), infliximab
- infliximab, ustekinumab (90 mg), adalimumab
- secukinumab, ustekinumab (90 mg), infliximab
- ustekinumab (45 mg), adalimumab, infliximab
- ustekinumab (90 mg), adalimumab, infliximab.

4.14 It heard from the clinical experts that the sequences of treatment included in the company's economic model mostly reflected current practice in the NHS, except that etanercept and infliximab were not used as a first biological treatment. Also, depending on the weight of the patient, ustekinumab 90 mg may be used as a second biological

treatment if there is an inadequate response to ustekinumab 45 mg. This sequence was not included in the company's economic model. The committee also considered whether ixekizumab would replace an existing biological treatment, or extend a sequence of biological treatments. It heard from clinical experts that although ixekizumab could initially extend an existing biological treatment sequence, over time as more data become available it may replace an older, less efficient biological treatment. The committee recognised that the treatment sequences presented did not cover all possible sequences but concluded that the sequences included by the company in its economic model reasonably represented current NHS practice.

## Modelling utility benefit

- 4.15 The committee understood that the company had used the subgroup of patients with a DLQI of more than 10 from the UNCOVER trials to estimate utility benefit. It noted that this differed from the intention-to-treat populations (that is, those with a DLQI ranging from 0 to 30) from the UNCOVER trials and from other trials included in the company's network meta-analysis, that were used to model treatment effectiveness. The committee acknowledged that this subgroup could not be used to model treatment effectiveness because not all the trials included in the network meta-analysis reported subgroup data. It accepted that because the subgroup population with a DLQI of more than 10 represented the patients seen in clinical practice, it was appropriate to analyse this subgroup where possible. It concluded that it was therefore appropriate to use this subgroup of patients to estimate utility benefit.
- 4.16 The committee considered when patients would get the benefit of treatment, and when to apply the utility gains from treatment in the model. It was aware that the company had applied utility gains in the maintenance period of treatment, but not the induction period. It heard from both the ERG and the company that ixekizumab is associated with a rapid response and therefore utility gains during the induction period were likely. The committee concluded that it would be appropriate to include utility gains for ixekizumab in the induction period, and that excluding this underestimates the quality-adjusted life year (QALY) gain associated with ixekizumab.

4.17 The committee noted that the company did not include the disutility of adverse events in its model. It considered that this did not reflect the importance of manageable side effects (see [section 4.1](#)). It heard from the company that there were little data available on severe adverse events that led to stopping treatment. The committee heard from the clinical experts that biological treatments were generally well tolerated (see [section 4.10](#)) and that their side effects profiles were similar, and concluded that it was therefore acceptable to exclude the adverse events in the model.

## Costs of adverse events

4.18 The committee acknowledged that serious adverse events including non-melanoma skin cancer, malignancies other than non-melanoma skin cancer and severe infection did not occur very often (see [section 4.10](#)). However, the committee considered that it was appropriate to capture all the benefits and costs, including the costs of adverse events over the time horizon of the model. The committee concluded that the company should have included the costs of adverse events in its economic model, particularly given that the quality-of-life data were likely to already include any disutility from adverse events.

## Costs of best supportive care

4.19 The committee noted that the costs of best supportive care had been estimated used the Fonia et al. (2010) study. It was aware from previous appraisals for psoriasis that when this study had been used, the conclusion was that it was likely to overestimate the costs of best supportive care. The committee understood from the ERG's analysis that if the costs of best supportive care were lower, the incremental cost-effectiveness ratios (ICERs) for ixekizumab compared with other biological treatments would increase. It considered that the estimates from Fonia et al. do not represent best supportive care after many biological treatments have not worked because they include costs of systemic treatments that are unlikely to be given after 3 biological treatments. The committee concluded that the costs of best supportive care remained uncertain, but given that data are lacking in this area, considered that the Fonia et al. estimates were appropriate for the



company to use in the economic model.

## Results of cost-effectiveness analysis

- 4.20 The committee noted that the company had given deterministic results in its base case. The committee preferred to use a probabilistic base-case analysis for decision-making. It agreed that the cost of adverse events should be included and that utility gains should be applied in the induction period of treatment, which the ERG had done in its base-case analysis. The committee noted that the ERG had also fixed errors in the company's model for adverse event rates and costs, calculating the standard error for NHS reference costs, and calculating the number of doses of secukinumab in the maintenance period. The committee therefore preferred to consider the results of the ERG's base-case analysis in its decision-making.
- 4.21 The committee noted that when validating the company's model, the ERG's ICERs for each comparator alone (that is, not in a sequence with other treatments) compared with best supportive care were more than £30,000 per QALY gained. The committee considered that including potentially non-cost-effective comparators, especially within sequences of treatments could result in misleading ICERs. The committee therefore also took into account comparisons against best supportive care in its decision-making. It noted that the ERG had presented analyses with ixekizumab at different positions within the treatment pathway (as the first biological treatment or as the second), and considered each in turn.
- 4.22 The committee considered the cost-effectiveness analyses for ixekizumab as the first biological treatment in a treatment sequence, taking into account the patient access schemes associated with ixekizumab and secukinumab. It noted:
- The incremental analysis included sequences with etanercept and infliximab as the first biological treatments in a sequence, which the committee heard does not represent current clinical practice (see [section 4.14](#)). The analysis also included a sequence which included ixekizumab as the second biological treatment in a sequence, which also does not represent current clinical practice. The committee therefore concluded that it would not use this analysis

for decision-making.

- Pairwise comparisons of the relevant sequences showed that ixekizumab as the first biological treatment in the treatment pathway either dominated other biological sequences (was more effective and cost less), or the ICERs for that sequence were less than £30,000 per QALY gained.

4.23 The committee considered the cost-effectiveness analyses for ixekizumab as the second biological treatment in a treatment sequence, taking into account the patient access schemes associated with ixekizumab and secukinumab. It noted:

- The incremental analysis included sequences that do not represent current clinical practice (see section 4.22), so the committee concluded that it would not use this analysis for decision-making.
- Pairwise comparisons of the relevant sequences showed that the sequence including ixekizumab dominated all other treatment sequences. The exception was the comparison with the sequence of secukinumab followed by ustekinumab and infliximab because the sequence of adalimumab followed by ixekizumab and infliximab had fewer total costs and QALYs than the sequence including secukinumab. The committee was aware that, in a sequencing model, the costs and benefits are driven by all the treatments in the sequence. It noted that the ICER for the sequence including ixekizumab compared with the sequence including secukinumab was more than £50,000 saved per QALY lost.

4.24 The committee considered the cost-effectiveness analyses for ixekizumab (not in a sequence) compared with best supportive care, and the ICERs for each comparator (not in a sequence) compared with best supportive care, which were used by the ERG to validate the model (see section 4.21). The committee recognised these analyses used the company's assumptions. It noted:

- Pairwise comparisons of the other biological treatments compared with best supportive care gave ICERs in the range of £46,000 to £74,000 per QALY gained.
- Pairwise comparison of ixekizumab compared with best supportive care gave an ICER of £41,000 per QALY gained. The committee therefore concluded that the cost effectiveness of ixekizumab was similar to that of other biological

treatments when compared with best supportive care.

- 4.25 The committee was aware that the company had not explored the full range of treatment sequences that might be offered in current NHS practice (see [section 4.14](#)). The committee recognised that best supportive care was not a relevant comparator given the position of ixekizumab in the treatment pathway, but it considered the comparison in its decision-making to account for potential bias from including non-cost-effective comparators within all other analyses. The committee considered the cost effectiveness of ixekizumab in the light of previous appraisals in this disease area and concluded that the most plausible ICER was likely to be in line with the other biological treatments already recommended in previous NICE guidance. The committee concluded that the ICER was within the range that could be considered a cost-effective use of NHS resources.

## Stopping rule

- 4.26 The committee was aware that previous appraisals for treating psoriasis recommended stopping treatment if there was an inadequate response; an adequate response was defined as either a 75% reduction in the PASI score from when treatment started, or a 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started. The latter stopping rule was originally included based on clinical advice, rather than specific evidence on the clinical- and cost effectiveness of this treatment strategy. The committee agreed that if there was no response to ixekizumab, the patient should not continue treatment. The committee noted that PASI 75 was the primary outcome in the trial data used to model the cost effectiveness of ixekizumab. It also considered the cost-effectiveness evidence for a PASI 50 stopping rule submitted by the company as a scenario analysis during consultation. It noted that the cost effectiveness of ixekizumab improved when a PASI 50 stopping rule was applied. The committee thought this may be counter-intuitive because there would be a smaller benefit for those with a PASI 50 response for the same cost. It heard from the company that, when the PASI 50 stopping rule is applied, patients remain on ixekizumab for longer, which increases the benefit accrued from having active treatment. The committee acknowledged that the sequencing model

made it difficult to ascertain what was driving the results. The committee appreciated that, in patients with psoriasis affecting their hands and feet, a PASI 75 may be difficult to achieve because gains in quality of life from having treatment could represent clinical improvement but not be accounted for in the PASI score. The committee therefore concluded that, for consistency with previous appraisals for biological treatments in psoriasis, ixekizumab should be stopped if there is an inadequate response at 12 weeks, with an adequate response defined as a 75% reduction in the PASI score from when treatment started or a 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started.

## Innovation

- 4.27 The committee considered whether ixekizumab was an innovative treatment. It heard from the clinical experts that ixekizumab did not differ substantially in its mechanism of action from secukinumab. The committee concluded that the company had not given the committee any additional evidence of benefits that were not captured in estimating the QALYs.

## Equality issues

- 4.28 The committee noted the potential equality issues raised in the consultee submissions, that the PASI can underestimate disease severity in those with darker skin, and that the DLQI has limited validity in older people and those not working, and may also miss anxiety and depression. The committee concluded that when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate. Also, it concluded that when using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

## Pharmaceutical Price Regulation Scheme (PPRS)

## 2014

4.29 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

## Summary of appraisal committee's key conclusions

TA442	Appraisal title: ixekizumab for treating moderate to severe plaque psoriasis	Section
<b>Key conclusion</b>		
Ixekizumab is recommended as an option for treating plaque psoriasis in adults, only if: <ul style="list-style-type: none"> <li>• the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10</li> <li>• the disease has not responded to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them, and</li> <li>• the company provides the drug with the discount agreed in the patient access scheme.</li> </ul>		1.1
The committee concluded that ixekizumab was more clinically effective than placebo and etanercept.		4.7

<p>The evidence review group's (ERG's) pairwise comparison of ixekizumab as the first biological treatment in the treatment pathway compared with other relevant sequences showed that ixekizumab either:</p> <ul style="list-style-type: none"> <li>• dominated other biological sequences (was more effective and cost less) or</li> <li>• the incremental cost-effectiveness ratios (ICERs) for that sequence were less than £30,000 per quality-adjusted life year (QALY) gained.</li> </ul>	4.22	
<p>Pairwise comparisons of the relevant sequences showed that the sequence including ixekizumab as the second biological treatment dominated all other treatment sequences. The exception was the comparison with the sequence of secukinumab followed by ustekinumab and infliximab because the sequence of adalimumab followed by ixekizumab and infliximab had fewer total costs and QALYs than the sequence including secukinumab. However, the committee noted that the ICER for the sequence including ixekizumab compared with the sequence including secukinumab was more than £50,000 saved per QALY lost.</p>	4.23	
<p>The committee concluded that the ICER was within the range that could be considered a cost-effective use of NHS resources.</p>	4.25	
<p><b>Current practice</b></p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Clearing symptoms with treatments associated with few or manageable side effects is important to people with psoriasis, as is having a choice of treatments.</p>	4.1
	<p>Biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin, methotrexate and PUVA) or when these treatments are contraindicated or not tolerated.</p>	4.2
<p><b>The technology</b></p>		

Proposed benefits of the technology	The results of the 3 UNCOVER trials showed that ixekizumab is more clinically effective than placebo and etanercept.	4.7
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Treatment with biologicals is generally well tolerated and the tolerability of ixekizumab was considered to be similar to that for other biological treatments.	4.10
What is the position of the treatment in the pathway of care for the condition?	Ixekizumab is likely to be primarily offered to patients whose disease has not responded to a previous biological treatment and to patients who cannot have other biological treatments.	4.2
Adverse reactions	The most common adverse reactions with ixekizumab in clinical trials were upper respiratory tract infection and injection site reactions.	2
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The evidence mostly came from 3 trials: UNCOVER-1, -2 and -3, which were double-blinded, randomised controlled trials that included a total of 3,866 patients. UNCOVER-1 compared ixekizumab with placebo, and UNCOVER-2 and -3 compared ixekizumab with placebo and with etanercept.	4.4
Relevance to general clinical practice in the NHS	The committee concluded that the patients in the UNCOVER trials were representative of patients seen in the NHS who would be considered for biological treatment, and so the results were generalisable to patients in the NHS.	4.5, 4.6

Uncertainties generated by the evidence	The dose of etanercept given in the trials was double that which is recommended NICE's technology appraisal guidance on <u>etanercept and efalizumab for the treatment of adults with psoriasis</u> , and was considered by the clinicians to be more effective than lower doses of etanercept. Therefore the committee considered that the treatment effect of ixekizumab compared with etanercept could be underestimated.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The benefit of treatment with ixekizumab compared with placebo and etanercept could be seen in the subgroup of patients who had already had biological treatment, as well as those who had not previously had biological treatment. The committee noted that the trials were not powered to detect statistically significant differences between subgroups, and so could not be certain that the treatment effect of ixekizumab did not differ across these subgroups, but agreed there was no evidence of a subgroup effect.	4.8
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Patients randomised to ixekizumab had clinically and statistically significantly higher PASI 75 response rates (that is, a 75% reduction in PASI score from when treatment started) at week 12 than placebo and etanercept.	4.7
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The company presented a Markov state transition model comparing a treatment sequence with ixekizumab given as the first in a sequence of 3 biological treatments, with 6 other biological treatment sequences.	4.11, 4.13



Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that the treatment sequences included by the company in its economic model reasonably represented current NHS practice, although it heard that 2 of the treatment sequences are not used in current practice.	4.14
	The committee concluded that the company should have included the costs of adverse events in its economic model.	4.18
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee concluded that it would be appropriate to include utility gains associated with treatment benefit in the induction period, and not just in the maintenance period.	4.16
	The company had not given the committee any additional evidence of benefits that were not captured in estimating the QALYs.	4.27
What are the key drivers of cost effectiveness?	<ul style="list-style-type: none"> <li>• Treatment sequences included.</li> <li>• Utility benefit and when it is applied.</li> <li>• Costs of adverse events.</li> <li>• Costs of best supportive care.</li> </ul>	4.14, 4.16, 4.18, 4.19

Most likely cost-effectiveness estimate (given as an ICER)	The ERG's pairwise comparison of ixekizumab as the first biological treatment in the treatment pathway compared with other relevant sequences, showed that ixekizumab either dominated other biological sequences), or the ICERs for that sequence were less than £30,000 per QALY gained. Pairwise comparisons of the relevant sequences showed that the sequence including ixekizumab as the second biological treatment dominated all other treatment sequences. The exception was the comparison with the sequence of secukinumab followed by ustekinumab and infliximab because the sequence of adalimumab followed by ixekizumab and infliximab had fewer total costs and QALYs than the sequence including secukinumab. However, the committee noted that the ICER for the sequence including ixekizumab compared with the sequence including secukinumab was more than £50,000 saved per QALY lost.	4.22, 4.23
	The committee concluded that the ICER was within the range that could be considered a cost-effective use of NHS resources.	4.25
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	The company presented analysis that included the confidential patient access scheme for ixekizumab. The ERG presented analysis that included the confidential discounts for both ixekizumab and secukinumab.	–
End-of-life considerations	Not applicable.	–
Equalities considerations and social value judgements	When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.	1.3
	When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.	1.4

## 5 Implementation

- 5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe psoriasis and the doctor responsible for their care thinks that ixekizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Eli Lilly have agreed that ixekizumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [UKPricing@lilly.com](mailto:UKPricing@lilly.com).

## 6 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

### NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Technical Lead

#### **Jasdeep Hayre and Ahmed Elsada**

Technical Advisers

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